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An Association between Anti-Phospholipid Antibodies and Connective Tissue Diseases

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Abstract

Background: Anti-phospholipid antibodies (APLA) are mostly directed against phospholipids and also with their binding proteins. They are frequently associated with connective tissue disorders. Systemic Lupus Erythematosus (SLE) associated with APLA might cause diagnostic dilemma due to several manifestations mainly neurological, serositis proteinuria, thrombocytopenia, haemolytic anemia, ulceration of legs, which occur in both the conditions. So, we had conducted a study to determine the association between anti-phospholipid antibodies and connective tissue diseases and also compared clinical and laboratory parameters between anti-phospholipid antibody positive and anti-phospholipid antibody negative groups. **Subjects and Methods:** The present study was conducted among two hundred and four patients who were diagnosed with connective tissue diseases. APLA testing was done at baseline and the patients who were found to be positive for the test, a repeat of the test was performed after 12 weeks. **Results:** Among the patients with connective tissue diseases (14 p.c) had a positive test result for anti-phoshpolipid antibodies. In the SLE group positive anti-phospholipid antibody was detected among 73.3 p.c of patients, mixed connective tissue disease (MCTD) was present among 13.3 p.c of the patients and systemic sclerosis was present among 13.3 p.c of the patients. **Conclusion:** Always an anti-phospholipid antibody test should be conducted among all the patients with connective tissue disease for early diagnosis and prevention of life-threatening complications.

Keywords: Anti-phospholipid antibodies, Connective tissue disease, SLE.

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Introduction

Anti-phospholipid antibodies (APLA) are the heterogeneous family of plasma autoantibodies which recognize the antigenic epitopes carried by phospholipoproteins.[1] Anti-phospholipid antibody syndrome (APS) is a thrombotic disorder, defined by the presence of one (or) more clinical features of thrombosis and presence of anti-phospholipid antibodies (APLA) such as anti-cardiolipin (aCL), anti-b2GP1 and lupus anticoagulant (LA).[2,3] APS is mostly associated with an underlying autoimmune disorder such as Systemic Lupus Erythematosus (SLE), the underlying disorder is not identified in primary APS.[4,5] Anti-phospholipid antibody (APLA), which occur secondary to Systemic Lupus Erythematosus (SLE) and other autoimmune diseases is termed as secondary anti-phospholipid antibody syndrome which is characterized by arterial and venous thrombosis, recurrent miscarriages during pregnancy and neurological manifestations.6 APLA are prevalent in patients with SLE (50 p.c) with LA (15-34 p.c) and aCL (12-30 p.c) approximately.7 Systemic Lupus Erythematosus (SLE) associated with APLA might cause diagnostic dilemma due to several manifestations mainly neurological manifestations, serositis proteinuria, thrombocytopenia, haemolytic anemia, ulceration of legs, which occur in both the conditions.8 Due to the presence of less number of studies, we had planned to conduct a study to determine the association between anti-phospholipid antibodies and connective tissue diseases and also compared clinical and laboratory parameters between anti-phospholipid antibody positive and anti-phospholipid antibody negative groups.

Aim & Objectives

1. To determine various aetiologies associated with connective tissue diseases.
2. To estimate the connective tissue diseases positive for APLA (aCL and LA).
3. To determine the association between clinical manifestations and APLA.

Subjects and Methods

This is a hospital based, analytical cross-sectional study, was conducted among two hundred and four patients who were diagnosed with connective tissue disorders like Systemic Lupus Erythematosus, Mixed Connective Tissue Disease (MCTD), Sjogrens syndrome and systemic

sclerosis based on clinical criteria and laboratory parameters obtained. The updated Sapporo APS Classification or Sydney Classification (2006) for clinical criteria and laboratory criteria were used to classify the patients.9 The study was started after obtaining clearance from the Institutional Ethics Committee (IEC) and a written consent was taken from the patients. Those who had given written consent to participate in the study were included. A detailed history taking and clinical examination was performed. All the patients were subjected to undergo routine blood tests mainly complete hemogram with peripheral smear, renal function tests, urine routine examination, liver function tests, Coomb's test, anti- nuclear antibody testing, extracted nuclear antigen testing and a skin biopsy. A Chest X-ray, Electrocardiogram (ECG), Echocardiogram (2-D Echo), and Pulmonary Function Tests (PFT) were performed on the patients. A computed tomography brain (CT-Brain) and Doppler study of lower limbs was performed among selected indicated patients. APLA test (which included anti-cardiolipin antibody and LA tests) was performed as a baseline test to all the patients and patients who were found to be positive for the test, a repeat of the test was performed after 12 weeks as per the international consensus statement in revised classification criteria for definite APS. To detect LA an automated coagulation analyzer was used which was based on coagulation tests and test was considered positive if the results showed >1.2 s (normal value is less than or equal to 1.2 s). To detect aCL, ELISA method was done and it was considered positive if results showed >12 u/ml (normal value is less than or equal to 12 u/ml).

Results

In the present study two hundred and four patients were included and [Table 1 & Figure 1] show 54 p.c (110) were diagnosed with SLE followed by 18.3 p.c (38) were diagnosed with MCTD, 15.7 p.c (32) were diagnosed with systemic sclerosis and 12 p.c (24) were diagnosed with Sjogrens syndrome. In Table-2 the APLA positive patients with SLE were 73.3 p.c (23) subjects followed by 13.35 (4) p.c in systemic sclerosis and 13.35 p.c (4) MCTD. The aCL positive patients with SLE 5.5 p.c (9) followed by 3.7 p.c (2) in systemic sclerosis and MCTD each. The LA positive patients with SLE 9.5 p.c (14) followed by 3.7 p.c (2) in systemic sclerosis and MCTD each. In Table-3 the percentage of APLA positivity and APLA negativity patients with neurological manifestations, hemolytic anemia, leg ulcers, thrombocytopenia, proteinuria and serositis were overlapping between APLA and connective tissue disorders had been tabulated with statistical values. The patients who were with above clinical manifestations and positive for APLA belonged to the SLE group.

Table 1: Distribution Of Patients Based On Diagnosis

Diagnosis	Number of patients	Percentage of patients
SLE	110	54
MCTD	38	18.3
Systemic sclerosis	32	15.7
Sjogrens syndrome	24	12
Total	204	100

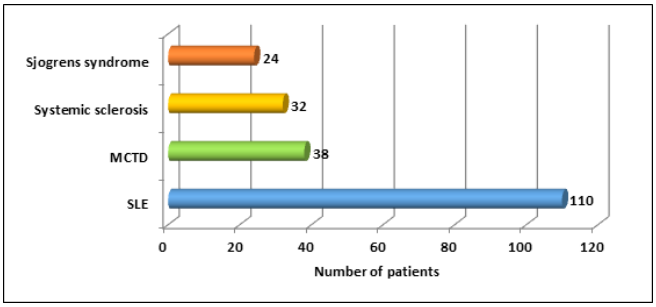

Figure 1: Distribution of Patients Based on Various Etiologies

Table 2: Connective Tissue Etiologies and Percentage of Positive APLA, ACL and LA among the Patients

Etiology	Percentage of APLA Positive Patients	aCL Positive Patients	LA Positive Patients
SLE	73.3 (23)	5.5 (9)	9.5 (14)
Systemic sclerosis	13.35 (4)	3.7 (2)	3.7 (2)
MCTD	13.35 (4)	3.7 (2)	3.7 (2)

Table 3: SLE Patients with Clinical Manifestations and Percentage of Positive & Negative APLA among Patients

Clinical manifestations	Percentage of APLA Positive Patients	Percentage of APLA Negative Patients	p-Value
Neurologic manifestations	72.7	27.3	0.01
Hemolytic anemia	62.3	37.7	0.001
Leg ulcerations	87.2	12.8	NS
Thrombocytopenia	72.7	27.3	NS
Serositis	25.8	74.2	NS
Proteinuria	19.6	80.4	NS

Discussion

The vessel wall integrity will be maintained by anti-phospholipid antibodies which are directed against cell membrane phospholipids. Manifestations like neurological, hemolytic anemia, thrombocytopenia, leg ulcerations, proteinuria and serositis are overlapping in APLA and connective tissue disorders most importantly among patients with SLE, which cause a diagnostic dilemma. In a study conducted by Cervera R and Piette JC et al in the year 2002, APLA positivity was found to be among 36.2 p.c in the SLE group.[10] In the present study, 73.3 p.c of patients with positive APLA belonged to the SLE group. In this study about 87.2 p.c SLE patients were suffering from leg ulcerations had a positive APLA. Similar to the study by Yoon KH et al., 49.3 p.c of APLA positive SLE had neurological manifestations.[11] In the present study, 72.7 p.c of APLA positive SLE patients had neurological manifestations. In a study conducted by Nesher G et al, 89 p.c SLE patients presented with thrombocytopenia and there was a statistically significant association between thrombocytopenia and APLA positivity.[12] Similarly in the present study, 72.7 p.c with thrombocytopenia were APLA

positive but there was no statistically significant association between thrombocytopenia and SLE. In the present study serositis, leg ulcerations, thrombocytopenia and proteinuria were overlapping between SLE and APLA, but there was no statistically significant association between these manifestations and APLA positivity.

Conclusion

Anti-phospholipid antibodies and SLE have overlapping clinical manifestations. APLA can complicate SLE further which results in higher morbidity rates. So, it is important to detect APLA for early diagnosis and prevention of life-threatening complications among patients suffering from connective tissue disorders most importantly SLE.

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